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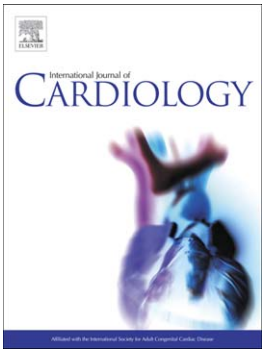

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Clinical Risk Factors and Subclinical Target Organ Damage as Predictors of New-onset of Atrial Fibrillation: the Catanzaro Atrial Fibrillation Project

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*All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Atrial fibrillation (AF) is the most common cardiac rhythm disorder in adult and old subjects with an increased risk for stroke, mortality and hospitalizations with a significant impact on the health care economic costs [1]. Several clinical conditions are recognized as risk factors for AF [2] and they are able to significantly increase the risk of future cardiovascular (CV) events [3].

In clinical practice the subclinical target organ damages (TOD) is considered a strong and independent predictor of CV events, in particular the measurements of carotid intima-media thickness (IMT), left ventricular hypertrophy (LVH) and chronic kidney disease [4-6]. There are no data demonstrating that incident AF may occur in the general context of CV disease burden. Thus, in the present study we investigated in a large cohort of subjects, with different CV risk factors and TOD, the possible association between these factors and new onset AF, testing the hypothesis that CV risk factors and TOD predict new onset AF.

We performed a population-based prospective study aimed to assess the association between new AF and CV risk profile estimated by using the 10-year Framingham risk score (FRS) categories (low=0-10, intermediate=11-20, high=>20) and/or subclinical TOD presence. We enrolled 3549 Caucasian outpatients, 1829 men and 1720 women, aged 60.7$\pm$10.6 years without baseline AF. The local Ethics Committee approved the protocol and informed written consent was obtained from all participants. All the investigations were performed according with the principles of Declaration of Helsinki. TOD was defined as IMT value >0.9 mm by carotid ultrasonography, left ventricular mass >110 g/m^2 for women and >134 g/m^2 for men by echocardiographic measurements according to American Society of Echocardiography [7], and estimated-glomerular filtration rate (e-GFR)<60 ml/min/1.73m^2 by CKD-EPI equation [8].

During the follow-up (mean 53.3$\pm$18.1 months, range 20 –150), there were 546 new cases of AF (15.4%), accounting for an incidence of 4.5% per year. Progressors to new onset AF were older, had a higher body mass index, blood pressure, LDL-cholesterol, glucose, cardiac mass, and a lower e-GFR; also, hypertension, metabolic syndrome, diabetes, LVH and carotid wall thickening were more common among AF cases than controls. The 10-year mean FRS was higher in progressors

than non-progressors to AF. Moreover the prevalence of new onset AF increases from low to high FRS categories as well as with the increase of the number of subclinical TOD. A multiple Cox regression analysis demonstrated that independent variables associated with AF risk were body mass index (HR=1.02, 95%CI=1.00-1.03), intermediate FRS category (HR=1.64, 95%CI=1.26-2.14), carotid thickening (HR=2.00, 95%CI=1.69-2.37), high FRS category (HR=2.07, 95%CI=1.61-2.66), LVH (HR=2.29, 95%CI=1.88-2.78) and renal dysfunction (HR=2.48, 95%CI=2.06-2.99). In figure 1 the adjusted Kaplan-Meyer curves for incident AF across categories of single or multiple subclinical TOD is reported.

The analysis of ROC curves shows that the composite score including LVH, IMT and renal function produces a ROC curve area (AUC) of 0.74±0.01 for identifying patients who develop AF. This value is significantly higher (P<0.001) than AUC produced by the FRS (AUC:0.63±0.01), demonstrating that the clinical and biological plausibility of TOD is stronger than that of CV risk factors. Thus, the composite TOD score has the highest predictive value for discriminating patients with from those without new-onset AF. The interaction analysis among all three markers of subclinical TOD (renal, cardiac and vascular) in predicting the study outcome showed that these factors strongly interact in explaining the incidence rate of AF in the study population. A synergistic effect (that is an observed HR for AF higher than that expected in the absence of interaction under the additive model) was found for each combination of subclinical TOD, and was particularly strong when all three factors were simultaneously present in the same patient (Figure 2). The excess risk for AF caused by the interaction of all three markers of subclinical TOD (synergy index) was 4.5 times higher than that attributed to renal dysfunction, LVH and carotid wall thickening in the absence of interaction (P<0.001, AUC 0.74±0.01).

Present data clearly demonstrate that traditional CV risk factors, alone or in a cluster, which was even more evident for TOD, are significantly associated with new onset AF. The major clinical relevance is the evidence that AF may be considered a CV clinical manifestation in the context of CV risk profile. Moreover, this study has implications for screening for AF, especially among high

risk groups, and the need to consider early interventions to reduce the complications associated with AF.

The large sample size of the study population, the long duration of follow-up, and the results' persistent consistency in multiple analyses, adjusting for several confounders, confer an important validity to these data. Furthermore, the concordance with results obtained in the Rotterdam study [9], demonstrating a significant association between IMT and new-onset of AF in subjects without history of coronary artery disease, supports the biological plausibility of our data. In particular, TOD may well reflect the prolonged exposure to traditional CV risk factors perhaps suggesting that AF represents an intermediate step in the causal pathway of CV continuum, from CV risk factors to clinical events. In fact, atherosclerosis is very common in subjects with AF, and may be responsible for various clinical complications associated with AF, especially stroke and thromboembolism.

From a clinical point of view, present data have some important implications. TOD represents an established marker of prolonged exposure to many CV risk factors. It is likely that also the atrium might be damaged by the same CV risk factors, favouring the development of substrate obligatory for the appearance of AF. Based on this, the clinical spectrum of patients with AF is similar to that of patients with CV risk factors and at high risk of both AMI and stroke [10]. Thus, an aggressive and global treatment of subjects, with multiple subclinical disease, may contribute to lower the incidence of AF, consequently decreasing both the disease burden and costs of caring.

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FIGURE LEGENDS

Figure 1. Kaplan-Meier curves showing cumulative hazards of developing atrial fibrillation (AF), by single or multiple subclinical organ damage (TOD).

Data are adjusted for age, gender, LDL-cholesterol, systolic BP, BMI, and smoking status. Event rates are per 100 person-years. IMT=intima-media thickness; LVH=left ventricular hypertrophy; e-GFR=estimated glomerular filtration rate; F=female; M=male. Blue line=0 TOD; green line=1 TOD; yellow line=2 TOD; red line=3 TOD

Figure 2. Synergism between subclinical organ damage (TOD) for predicting atrial fibrillation (AF).

Expected and observed hazard ratios (HRs) for incident AF are represented by dashed and white bars, respectively. Interestingly, the excess risk caused by the interaction of all TOD (synergy index) was 4.5 times high, accounting for an observed HR of 13.354 (95%CI=9.751-18.290; P<0.0001). IMT=intima-media thickness; e-GFR=estimated glomerular filtration rate; LVH=left ventricular hypertrophy.

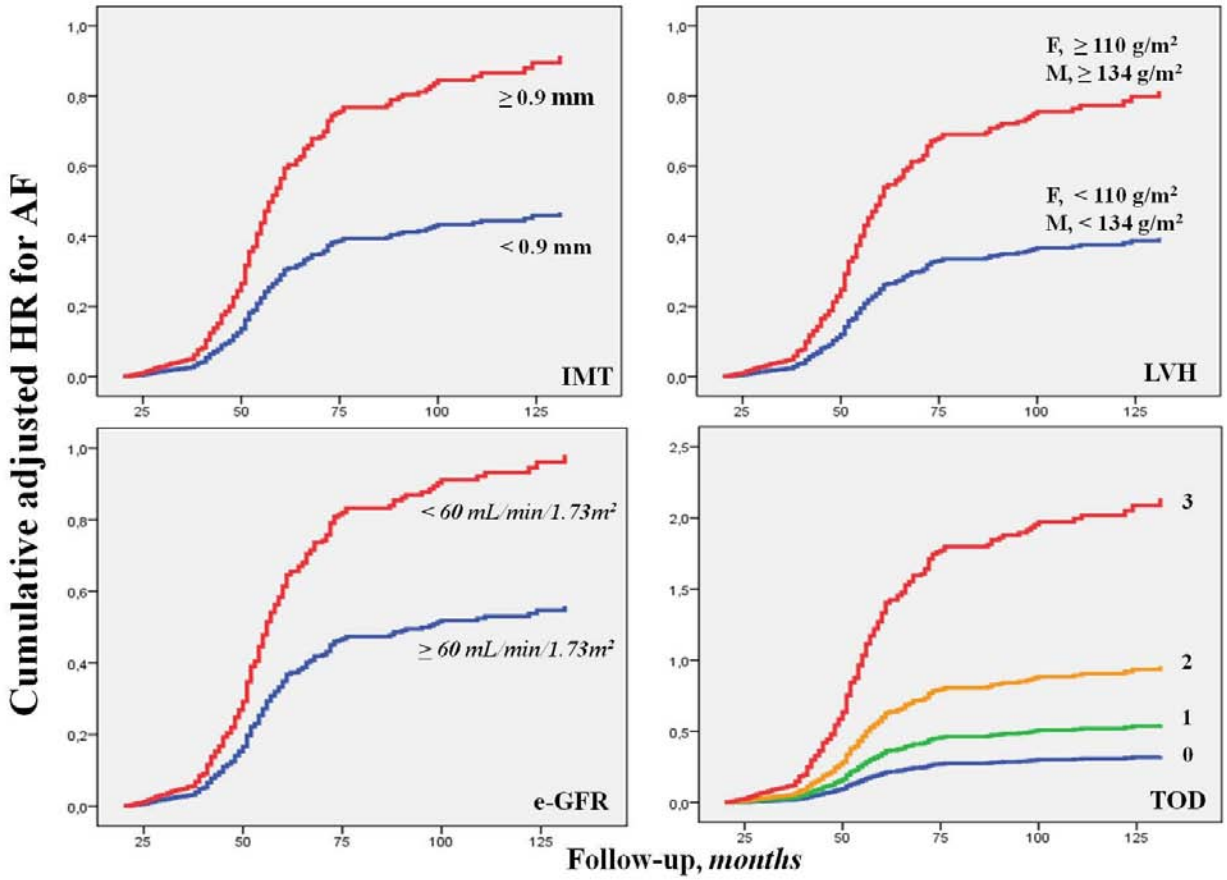

Figure 1

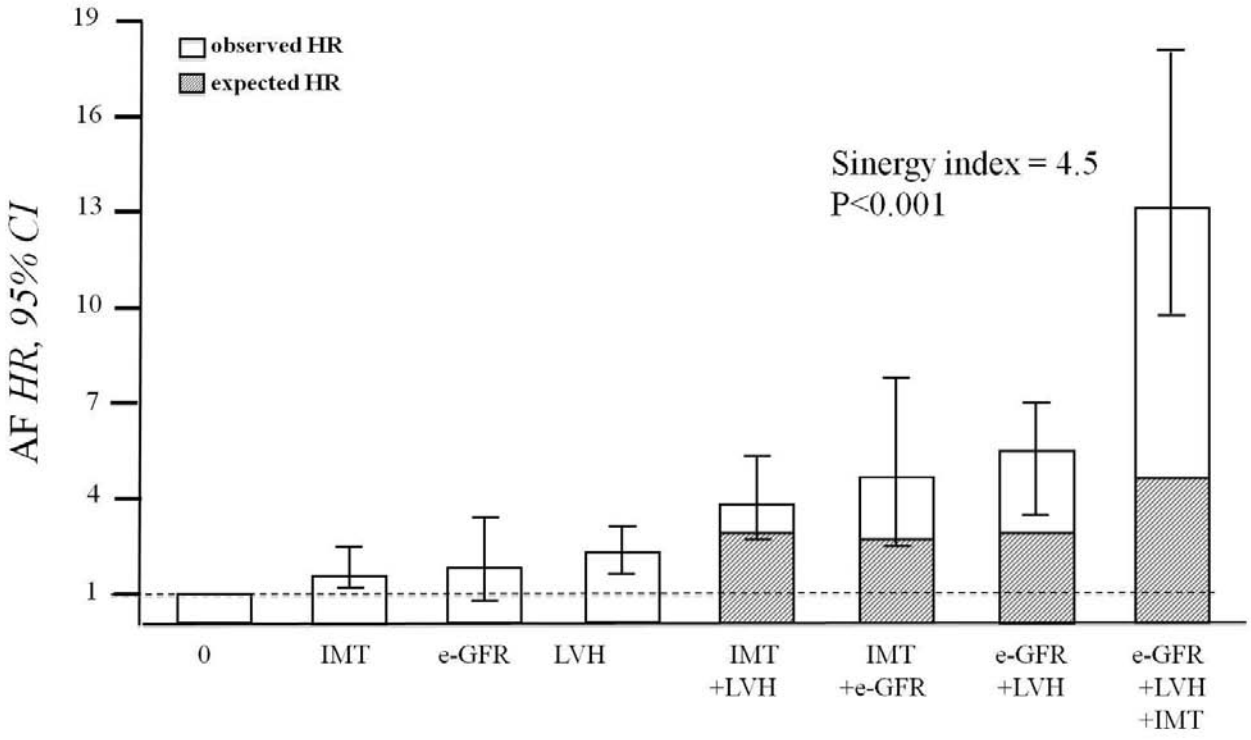

Figure 2